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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/591,224 | RUSSELL ET AL. | |
| | Examiner | Art Unit | |
| | KATHERINE SALMON | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,12-27,40-48 and 52* is/are pending in the application.

4a) Of the above claim(s) *18-27 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-17 and 40-48* is/are rejected.

7)☒ Claim(s) *1-10,12-17 and 40-48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/25/2008, 8/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of Group I and the species election of the SIRS inflammatory condition in the reply filed on 1/04/2010 is acknowledged. The traversal is on the ground(s) that (a) it would not be burdensome to examine all three indicated groups under MPEP 806.05(c) (p. 10 2nd paragraph). The traversal is also on the grounds that (b) gram positive infection would be expected to result in SIRS and therefore even if the elected inflammatory condition is SIRS it would still be a predictor of risk for gram-positive infection (p. 10 2nd to last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

(A) It is noted that MPEP 806.05(c) is related to the criteria of distinctness between combination and subcombinations. The instant case's restriction was based upon the guidance provided for 371 restrictions. Restrictions in 371 cases are based on unity of invention. Burden is not a factor in determining unity of invention. As set forth in the requirement for restriction, there is no special technical feature linking the recited groups as would be necessary to fulfill the requirement for unity of invention. As such there is neither requirement to show burden to examine nor a requirement for combination or subcombination.

(B) With regard to the traversal that gram positive infection would be expected to result in SIRS and therefore these two species are searchable together, this argument based upon the search of the prior art is persuasive. Specifically the art provided below discloses both SIRS and gram positive infection. As such the requirement for a species

election between these two inflammatory conditions has been withdrawn. However, the species election between the other inflammatory conditions presented in the claims is being maintained. As such, the species have only been search with regard to the elected species SIRS and gram positive infection.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-10, 12-27, 40-48, and 52 are pending. Claims 11, 28-39, 49-51, and 53-55 are cancelled.

3. Claims 18-27 and 52 are withdrawn as being drawn to a nonelected invention.

4. An action on the merits for claims 1-10, 12-17, and 40-48 is set forth below.

***Priority***

***5.*** If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an

international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the

information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

**In the present case**, it is further noted that the case claims priority to PCT/CA2005/000357 in the oath submitted 11/21/2008 however, the specification has not bee amended to list such priority in the first sentences of the specification and no ADS has been filed.

***Oath/Declaration***

***6.*** The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the citizenship of each inventor.

More particularly, it is noted that each inventor has listed his citizenship as "British Columbia." Although the examiner has considered treating this matter as an informality as a courtesy to applicant, the oath/declaration cannot be accepted because 35 USC 115 explicitly requires that applicant "shall state of what country he is a citizen."

### *Information Disclosure Statement*

7. The information disclosure statement (IDS) submitted on 8/31/2006 has been considered by the examiner.

The information disclosure statement filed 6/25/2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. It is noted that the reference of Sutherland on the IDS of 6/25/2008 has been considered by the examiner, as the art is used in the 35 USC 112 rejection recited below. As such a copy of the reference will be submitted with this action and therefore the applicant is not required to submit a legible copy.

### *Drawings*

8. The drawings submitted 8/31/2006 have been accepted.

### *Specification*

9. The disclosure is objected to because of the following informalities: On p. 38 line 14 of the specification a reference is referred to as "anonymous", correction should be made to clearly describe the article with which the specification is referring to by the appropriate author's name.

Further the specification is object to because all continuing data must be listed in the first paragraph of the specification if no Application data sheet has been filed.

Appropriate correction is required.

***Claim Objections***

10. Claims 1-10, 12-17, and 40-48 are objected to because of the following informalities: The phrase “increased at risk” in claim 1 line 2 is grammatically incorrect and should be amended to "increased risk of". The comma after “developing” in line 2 of claim 1 should be removed. Claims 2-10, 12-15, and 40-48 are objected to as depending from this objected claim.

Claims 14 and 17 are objected to as the claim lacks proper punctuation separating each item listed in the claim; see, for example, the recitation the inclusion of both a semicolon and a comma after injury in claim 14 line 6 and after abscess in line 7. Further the list is separated by semicolons throughout the list except for the last 4 lines where the conditions are separated by commons. The same punctuation should be used throughout the listing in the claims. These same issues are duplicated in Claim 17.

Claims 13 and 48 should be amended to correct a grammatical error. Specification, the phrase “defined as homozgosity” should be amended to “defined as homozygous”.

Claim 16 step b should be amended to remove the extra space in front of the

semicolon in the last sentence.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 1-4, 7-10, 12-17, 40-42, and 45-48 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to determining a genotype. This determining step could be a mental step. For example, claim 7 and 45 specifically list that the genotype can be determined by "reading sequence data". "Reading sequence data" would encompass determining a genotype by looking at a computer database.

The methods as claimed, do not meet the machine or physical transformation required by the CAFC court as described in *In re Bilski (*88 U.S.P.Q.2d 1385). The claims as written encompass mere mental steps i.e. determining the expression level of biomarkers, obtaining a plurality of sample probe intensities, or obtaining gene expression data from a microarray. The determining steps could be directed merely to looking at a database file on a computer (e.g. reading sequence data).

These rejections can be overcome by amending the claims to include steps of obtaining a sample.

***Claim Rejections - 35 USC § 112/2nd paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-10, 12-15, and 40-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10, 12-15, and 40-48 are indefinite. The terms "enhanced recovery" and “enhanced ability” in claim 1are a relative terms which render the claim indefinite. The term "enhanced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically it is not clear the degree of recovery which is required to be “enhanced”. For example it is not clear if recovery at a normal rate of time would be considered “enhanced”. As such the metes and bounds of the claim are not clear.

The term "poor” in claim 8 is a relative term which renders the claim indefinite. The term "poor" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically it is not clear which outcomes would be considered poor outcomes. For example having a treatable disease condition would be considered a poor outcome compared to not having a disease, but having an untreatable disease condition would also be considered

a poor outcome. As such it is unclear the degree of a "poor" outcome which must be observed to be considered within the metes and bounds of the claims.

The term "critically ill" in claims 9 and 12 is a relative term which renders the claim indefinite. The term "critically ill" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically it is not clear how ill a subject must be. For example it is unclear if the term would encompass any level of illness or if the claim requires some requisite degree of illness.

The terms "severe" and "less severe" in claims 9 and 12 are relative terms which render the claim indefinite. The terms "severe" and "less severe" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically if it not clear which cardiovascular or respiratory dysfunctions would be indicative of severe or less severe dysfunction. For example a normal level of cardiovascular dysfunction in a patient with sepsis would be more severe than a patient without sepsis but at the same time it would be less sever that a patient with full septic shock. Therefore the same condition could be considered both severe and less severe. As such the metes and bounds of the claims are not clear.

***Claim Rejections - 35 USC § 112/Scope of Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-10, 12-17, and 40-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (A) A method for determining an increased risk of developing gram positive sepsis infection comprising obtaining a sample from a human patient, determining the genotype at position 201 of SEQ ID No. 1 in the patient is an AA genotype, wherein the presence of AA indicates that the patient has an increased risk of developing gram positive sepsis infection compared to patients who have an AT or a TT genotype at position 201 of SEQ ID NO. 1. (B) A method for determining a decrease survival in a human patient infected with gram positive sepsis comprising obtaining a sample from a human patient who has systemic inflammatory response syndrome (SIRS), determining the genotype at position 201 of SEQ ID No 1 in the patient is a AT or TT, wherein the presence of AT or TT indicates that the patient has a decreased survival as compared to a patient who has an AA genotype, does not reasonably provide enablement for a determination of prognosis in any subject of enhanced recovery from any inflammatory condition or increased risk of developing any inflammatory condition by determining a genotype at one or more polymorphic sites in the toll-like receptor 2 (TLR-2) gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

It is noted that the enablement is drawn to the lack of predictably in associating any position or TLR2 with any inflammatory disease. The prior art has provided some associations of specific SNP positions in TLR2 with specific inflammatory conditions (see 35 USC 102(b) presented below), however, the prior art has not provided enabling support to the breadth of the claims. In order to provide compact prosecution the scope of enablement provided below is specific to the particular SNP and particular associations provided by the specification. As discussed below, neither the art nor the specification, however, provide a predictable correlation to any general SNP position of TLR2 and any general inflammatory condition.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The breadth of the claims

The claims encompass a correlation of prognosis in a subject of enhanced recovery from an inflammatory condition or increased risk of developing the inflammatory condition by detecting one or more polymorphic sites in the TLR-2 receptor. The claims are drawn to a protective genotype being predictive or indicative of enhanced ability to recover form the inflammatory condition and a risk genotype being predictive or indicative of an increased risk for developing the inflammatory

conditions.

The claims are further drawn to determination of one or more polymorphic sites which includes position 201 of SEQ ID No. 1 or a polymorphic site in linkage disequilibrium therewith.

The claims are drawn to correlations of the homozygous T genotype at position 201 of SEQ ID No. 1, the T allele at position 201 of SEQ ID NO.1 and the A allele at position 201 of SEQ ID No. 1.

The claims are drawn to inflammatory condition, and SIRs or gram positive associative inflammatory conditions in particular.

The claims are drawn to determining in critically ill subjects that association of the presence of protective or risk genotypes and severe or less severe cardiovascular or respiratory dysfunction.

As discussed below, although the specification is enabling for the specific scope of a particular SNP with a particular disease condition, the specification does not provide guidance for the breadth of the claims. Specifically the claims are towards prognosis of enhanced recovery or risk of developing an inflammatory condition by determining the genotype of any polymorphic site in TLR-2. As discussed below, the specification does not provide guidance for such breadth. Further the art discloses that such associations are species, diseases, and genotype specific. As such, the associations made in one particular correlation would not be predictive in for any other correlation.

The claims are drawn to polymorphism in linkage disequilibrium with positions

201 of SEQ ID NO. 1. As discussed below, the specification does not provide guidance to determine which polymorphic sites would have the same associations as a particular genotype at position 201 of SEQ ID No. 1. Further, the art discloses that associations in a particular SNP position do not provide specific correlation to any other polymorphism in linkage disequilibrium.

Nature of the Invention

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts that systemic inflammatory response syndrome (SIRS) is characterized by increased inflammation, increased coagulation, and decreased fibrinolysis (p. 1 lines 18-25). The specification asserts that Toll-like receptor 2 (TLR-2) has an important role in response to gram-positive bacteria (p. 1 lines 24-26).

The specification asserts that polymorphisms, such as Arg753Gln in TLR2 have been associated with susceptibility to staphylococcal infections in a septic shock population (p. 2 lines 3-6). As indicated by the art provided below the prior art does associate this specific SNP with susceptibility to staphylococcal infections in a septic shock population, however, this particular recitation of a SNP does not provide guidance for the breadth of the claims. In particular the art provided below teaches that not all SNPs are correlative to inflammatory conditions.

The specification discloses that human TLR-2 maps to chromosome 4 and extends over 2.6 kb (p. 2 lines 11-15). The specification asserts that one particular SNP is found at position 201 of SEQ ID No. 1 which represents a SNP that corresponds to -16934 relative to the TLR-2 transcriptional start site (p. 2 lines 12-20). The specification describes TLR-2 in relation to humans; however, the claims are drawn to any subject. Any subject would include associations to other species such as gorillas, cats, and dogs. It is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. Knowledge that mutations in a gene occur in one organism (i.e. humans) does not allow one to conclude that this gene and mutations in this gene will also occur in any other species and will be associated with inflammatory condition. The instant specification does not teach homologues of TLR-2 in a representative number of different organisms. Thus it would be unpredictable as to whether a polymorphism in TLR2 in a particular organism will be present in other organisms and will be associated with inflammatory conditions. As discussed below the art teaches that SNP associated with disease are species dependent (see teaching of Halushka et al.).

The specification asserts that TLR-2 SNP is associated with improved prognosis or subject outcome in subjects with an inflammatory condition (p. 3 lines 1-5). However, the specification provides not statistically significant correlation that the presence of any SNP, and in particular the SNP at position 201, is associated with improved prognosis of inflammatory condition.

The specification provides a very large list of potential inflammatory conditions

which includes a wide variety of diseases such as sepsis, septic shock, SIRs, tissue damage due to chemotherapy, arthritis, and congestive heart failure (p. 5-p. 6). Each inflammatory condition has a distinct association to the genotype of TLR-2. An association of one particular condition does not provide direct extrapolation of that association with any other inflammatory condition. For example the art (Jaen et al.) discussed below teaches that the SNP of Arg677Trp was not associated with the inflammatory condition or arthritis. As such statistically significant associations between a particular SNP and particular inflammatory conditions must be each individually tested and validated. There is no expectation of success for each of these associations as the art teaches that a structural difference in TLR2 is not sufficient for the predictable association to an inflammatory condition.

The specification asserts that identification is based upon the association with a decreased likelihood of recovery from an inflammatory condition (i.e. risk genotype) or an increased likelihood of recovery form an inflammatory condition (i.e. protective genotype) (p. 3 lines 6-10). However, these associations must be individually examined to determine if a particular genotype would be considered a risk, a protective, or a neutral genotype. These associations would further have to be examined for any of the myriad types of inflammatory conditions in multiple groups of species. The specification has not provided any guidance that such associations can be extrapolated between species, inflammatory conditions, or genotype structures. Further, as shown by the art, at the time of filing and even post-filing these broad correlations were unpredictable.

The specification asserts that the risk genotype may be an indication of an

increased risk of not recovering from an inflammatory condition and can including at least one T nucleotide at position 201 of SEQ ID NO. 1 (p. 9 lines 5-9). However, although there appears to be asserted associations of having an AT or TT and a decrease survival (p. 45 lines 1-5) not all associations to survival have been validated. Specifically Sutherland et al. (as discussed below) teaches that the genotype of AA at position 201 of SEQ ID No. 1 was not associated with survival. As such the art teaches that although some correlations might be predictive, the breadth of the claims is not predictable. Specifically even when the skill artisan examines only one polymorphic position of TLR2, the associations of the genotypes and inflammatory conditions can be directly extrapolated to one another.

Further, even at the site of position 201, the claims would encompass associations to three genotypes, AA, AT, and TT, and prognosis, recovery, or increased risk of developing an inflammatory condition. These associations must each be evaluated individually and the correlation of one association is not predictive of the correlation of any other association. In particular, as described in the paragraph above, and association of AT or TT with survival does not provide guidance that the genotype of AA is associated with survival. Specifically, even though the specification provides guidance that there is an association with decreased survival and AT or TT, the art (Sutherland et al), teaches there is no association between survival and AA.

The specification asserts that the polymorphic site may be at SNP 201 or any a polymorphic site in linkage disequilibrium thereto (p. 4 lines 11-12). The specification defines LD as the occurrence in a population of certain combinations of linked alleles in

greater proportion than expected from the allele frequencies at the loci (p. 17 lines 1-3). The specification does not teach any variants that are in linkage disequilibrium with the polymorphism at position 201. It is highly unpredictable if a polymorphism in linkage disequilibrium with the polymorphism at position 201 of SEQ ID NO. 1, 95%, 90%, 80%, 75% of the time will also be associated with an inflammatory condition. Specifically, the art (Wall et al. and Langdahl et al.) discussed below teaches that LD is not predictable and that there can be considerable variation between the frequencies at which alleles are inherited.

The claims are further drawn to broad terminology in which the specification has not provided any particular associations. The claims are drawn to "enhanced recovery". This term is not defined in the specification and it is not clear the difference between recovery and enhanced recovery. As such enhanced recovery would not only encompassed recovery from an inflammatory condition, but recover at a quicker pace. The specification has not provided guidance to determine if any of the polymorphic sites of TLR-2 are predictive of such a phenotype. Further, such an analysis would require many rounds of experimentation without a guarantee of success.

Working Examples

The specification does not provide a working example of the breadth of the claims, but rather, teaches correlations between particular inflammatory conditions and particular genotypes in a human patient.

Example 1 provides the haplotype of 223 patients who had at least two criteria

for sepsis (p. 41 liens 19-21). The specification provides different associations based upon this study.

Association 1. Increased rate of sepsis upon admission to the study (p. 43 lines 1-9).

The specification asserts that patients with a homozygous A genotype at position 201 had a relative risk of 1.3 of having sepsis on day 1 (95% CI= 1.1-1.6). This association appears to indicate that the rate of sepsis is increased in patients with AA genotypes as compared to patients with AT or TT genotypes. However, this association is not clear as it is not clear what phenotype is being examined by the specification. The specification asserts that there were more patients with the genotype of AA who had sepsis on day one of the observation period (p. 43 lines 1-5); however, it appears that all of the 223 patients have at least 2 or the 4 SIRs criteria for sepsis (p. 42 lines 23-27). The instant specification defines sepsis as the presences of at least two SIRS criteria (p. 21 lines 29-31). As such it appears that all the patients would be defined as having sepsis at the point of admission, regardless of the genotype.

Association 2. Association with predictive occurrence of gram positive cultures (p. 43 lines 10-22).

The specification asserts that patients homozygous for the A allele were twice as likely to have a gram positive culture as oppose to patients with AT or TT (RR=2.0, 95% CI=1.1-3.4). As indicated by the scope of enablement provided above, this association appears to be predictive. Further it is noted that post filing art of Sutherland et al., as discussed below, further confirmed this association.

Example 2 proves that the SNP position at 201 of SEQ ID No. 1 was examined in a cohort of 638 patients with SIRS (p. 44). The specification provides associations based upon this detection.

Association 3. Progressive decrease of survival

The specification asserts that there was a significant progressive decrease of survival in patients who were AA vs. AT or TT (p=0.0359). The specification asserts that patients with AT or TT had a decrease in survival versus patients with AA (p. 45 lines 1-5). As indicated in the scope of enablement, this association appears to provide a predictive correlation between patients with AT or TT genotypes and survivability. Although, Sutherland et al, discussed below, teaches that AA is not associated with increase survivability.

Association 4. Prevalence of sepsis on admission

The specification asserts that there was a progressive increase in prevalence of sepsis on admission to the ICU in patients who have TT, AT, and AA genotypes (p. 46 lines 1-5). However as discussed above, it appears that all the patients in the study had sepsis and therefore it is not clear what this association is towards.

Association 5. Days alive

The specification asserts that there was a significant association of T/A with days alive and free of cardiovascular dysfunction (p=0.019). An association with days alive and free of vasopressors (p=0.019) Days alive and free of inotropic agents (p=0.074) (p. 46 lines 1-15). The specification discloses that patients who carried AT or TT had more cardiovascular dysfunction shown as fewer days alive and free of cardiovascular

dysfunction, vasopressor use and inotropic agent use (p. 46 lines 1-15). The specification asserts that therefore patients with SIRS having a risk genotype (e.g. having a T allele) have an increase in cardiovascular dysfunction (p. 46 lines 6-15). Although the specification appears to show a correlation between the T alleles and cardiovascular dysfunction. The specification does not provide a validation study of this association. Further, study of this position and this phenotype indicates that this association is unpredictable. In particular Sutherland et al. teaches that there was no association of AA with septic shock or survival (discussed below). Sutherland further teaches that septic shock is defined by sepsis pulse significant hypotension or the need for vasopressors. As such the lack of an association with septic shock indicates that there is no association with the cardiovascular dysfunction or vasopressors associated with the phenotype.

Association 6. Days alive and free of 3 of 4 SIRs criteria

The specification asserts that there was a trend towards this association of patients with the T alleles (p=0.095) (p. 46 lines 17-20). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Association 7. Days alive and free of coagulation

The specification asserts that there was an association between A/T genotype and days alive and free of coagulation (p=0.048). The specification asserts that patients who carried the AT or TT had coagulation dysfunction shown in fewer days alive and

free of coagulation dysfunction (p. 47 lines 1-2). Although the specification appears to show a correlation between the T alleles and cardiovascular dysfunction. The specification does not provide a validation study of this association. Further, study of this position and this phenotype indicates that this association is unpredictable. In particular Sutherland et al. teaches that there was no association of AA with septic shock or survival (discussed below). Sutherland further teaches that septic shock is defined by sepsis pulse significant hypotension or the need for vasopressors. As such the lack of an association with septic shock indicates that there is no association with the cardiovascular dysfunction or vasopressors associated with the phenotype.

Association 8. Days alive and free of renal support and hepatic dysfunction

The specification asserts that there is a trend towards an association of renal support and days alive (p=0.082) and free of hepatic dysfunction (p=0.035) (p. 47 lines 1-10). Such that patients who carried the T allele had more hepatic dysfunction shown as fewer days alive and free of hepatic dysfunction (p. 47 lines 1-10). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Sepsis subgroup: The specification discloses that the T/A polymorphism was examined in 513 critically ill patients who had sepsis (p. 47 lines 10-20)

Association 9. The specification asserts that there was a trend toward a progressive decrease in 28 day survival amount AA, AT, TT genotypes groups (p=0.089) (p. 48 lines 4-5). It is noted that this association is not statistically significant.

Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype. Therefore this indicates that the combination of AA, AT, and TT does not provide a clear determination of survivability. Both the specification and the art indicates that there is only a predictive association to decrease survival with the detection of AT and TT as compared to AA individuals.

Association 10. Days alive and free of vasopression (p=0.049) and cardiovascular dysfunction (p=0.041), therefore patients who had sepsis and carried the T allele had more cardiovascular dysfunction shown as fewer days alive and free of cardiovascular dysfunction and vasopressor use.

Association 11. Trend of association of Days alive and free of 3 out of 4 SIRS criteria (p=0.082) and days alive and free of steroid support (p=0.092) (p. 49 lines 8-13). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Association 12. Trend for days alive and free of coagulation (p=0.084), free of INR (p=0.06), and free of hepatic dysfunction (p=0.066) (p. 49 lines 14-19). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Association 13. Trend between the genotype and days alive and free of respiratory dysfunction (p=0.071), free of mechanical ventilation (p=0.0999) (p. 49 lines 20-26). It is noted that this association is not statistically significant nor has it been

validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

The unpredictability of the art and the state of the prior art

It is also unpredictable as to whether the results obtained with SIRS, sepsis, and gram positive associated conditions can be extrapolated to other inflammatory conditions. The genus of inflammatory conditions is quite large and each condition has its own pathology and etiology. Given the differences in the causes and effect of each type of inflammatory disease, one can not extrapolate the results found in SIRS, sepsis, and gram positive associated conditions subjects to any type of inflammatory condition. For example, Jaen et al. (Arthritis Research and Therapy 2009 Vol.11:R5) teaches that rheumatoid arthritis is a common inflammatory condition (p. 1 1$^{st}$ paragraph). Jaen et al. teaches that there was no association between Arg677Trp (e.g. a TLR2 polymorphisms) and susceptibility to infection (p. 2 3$^{rd}$ paragraph). Jaen et al. teaches that there was no susceptibility to infection with the detection of Arg753Gln (e.g. a TLR2 polymorphism) (p. 2 3$^{rd}$ paragraph). As such the art teaches that the associations of polymorphism of TLR2 and inflammatory conditions are specific and that the breadth to associations with inflammatory conditions is unpredictable.

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. The art teaches that SNP associated with diseases are species dependent. Halushka (Nature Genetics, 1999; 22:239-247) teaches assessing the age or ancestral state of human SNP alleles by obtaining the

corresponding orthologous sequence from the closely related great apes (page 244, column 1, paragraph 2). Halushka teaches that although there was a high degree of sequence identity between great ape and human samples (page 244, column 2, paragraph 1), the average nucleotide divergence between human and chimpanzee, gorilla and orangutan was 0.010, 0.012 and 0.021, respectively, and that and that these values are more than ten times greater than the within-population human diversity (page 244, column 2, paragraph 1). Halushka teaches that the data suggest that 95% of population-specific SNPs arose in the human lineage after population differentiation and that the common allele [between human and ape] is the likely ancestral state.

Further it is highly unpredictable if a polymorphism in linkage disequilibrium with the polymorphism at position 201 of SEQ ID NO: 1, 95%, 90%, 80%, 75% of the time will also be associated with inflammatory conditions. This unpredictability is highlighted by the teachings of Langdahl (Journal of Bone and Mineral Research 2000 Vol 15 p. 402). Langdahl teaches that linkage disequilibrium between alleles is population dependent and there can be considerable variation between the frequencies at which alleles are inherited. For example the reference sites that while one group reported that a repeat polymorphism in the IL-1RN gene was in linkage disequilibrium with the IL-1B (+3§54) polymorphism, Langdahl et al were unable to show linkage between these polymorphisms. Additionally Wall (Nature Reviews Genetics 2003 volume 4, pages 587-597) teaches that linkage disequilibrium (LD) refers to the fact that particular alleles at nearby sites can co-occur on the same haplotype more often than is expected by chance (page 587, 1st column, 1st paragraph). Wall teaches that patterns of LD are

known to be noisy and unpredictable as pairs of sites tens of kilo bases apart might be in complete LD, whereas nearby sites from the same region can be in weak LD (page 587, 2nd column, last paragraph). Wall teaches that population history, population size, and population structure lead to differences in LD (page 588, 1st column, top). Wall teaches, “Measuring LD across a region is not straightforward" (box 1, last paragraph, page 588). Wall teaches it is difficult to compare results from different LD studies directly because of the variation in study design and methods of analyzing the data (page 591, 2nd column, 1st full paragraph). Wall teaches there are clear differences in LD between African’s and non-Africans (page 593, 1st column). Thus Wall teaches that LD is not predictable. As such both Langdahl and Wall demonstrate the unpredictability in associating a polymorphism in linkage disequilibrium with the polymorphism at position 201 of SEQ ID NO: 1 as a means for selecting a subject with an association to an inflammatory condition.

The art teaches that the association of particular polymorphic regions and sepsis is specific to the type of sepsis. Woehrle et al. (Cytokine 2008 VOl. 41 p. 322) that of the 325 patients with sepsis and septic shock associated with gram positive bacteria, none were positive to the SNP Arg677Trp (p. 324 2$^{nd}$ column 4$^{th}$ paragraph). Woehrle et al. teaches that association of SNPs and sepsis might be bacteria type dependent. Woehrle et al. teaches that Arg753Gln heterozygous patients were associated with Candida included sepsis but not Gram-positive sepsis (p. 328 1st paragraph). As such the type of sepsis (e.g. which bacteria the sepsis is from) would effect the correlation of

the phenotype to the genotype. Specifically in this case, the associations of the particular polymorphic position were observed in gram positive sepsis.

Post-filing art teaches that even with the specific polymorphic position of 201 of SEQ ID No. 1 each association to inflammatory condition must be individually examined and validated. Sutherland (Crit Care Med 2005 VOl. 33 p. 638) teaches that patients were used which had at least 2 of the 4 SIRs criteria and therefore were considered critically ill (p. 639 2nd column 2nd paragraph). Sutherland et al. teaches that these patients were genotyped for polymorphisms in TLR2 (p. 639 2nd column 3rd paragraph). Sutherland et al. teaches the detection of the same SNP region as the instant specification (-16933 T/A SNP) (p. 640 1st paragraph). Sutherland et al. teaches that TLR2 -16933AA was associated with significant increased prevalence of sepsis on admission to the ICU ($p < 0.03$ Figure 7) and specifically with increased prevalence of Gran positive infections ($p=0.04$) (p. 641 1st column last paragraph-2nd column 1st paragraph). Sutherland et al. teaches that AA was not associated with increased prevalence of positive bacterial cultures or septic shock on admission to the ICU or with a significant difference in 28 day survival (p. 641 2nd column 1st paragraph). The association to prevalence of sepsis on admission to the ICU is still unclear in the art as it is not clear what defines a patient as having sepsis. Sutherland et al. teaches that the patients admitted all had at least 2 or the 4 SIRs criteria. Sutherland et al. teaches that Sepsis was defined as the presence of two or more SIRS criteria plus the presence of a known or suspected infection during the 24 hour period (p 639 3rd column 2nd

paragraph). Therefore it appears that having two or more SIRS criteria defines the whole population studies as having sepsis.

Sutherland et al. teaches that septic shock was defined by sepsis plus significant hypotension such as systolic blood pressure or the need for vasopressors (p. 639 3rd column 3rd paragraph). Sutherland et al. teaches that AA was not associated with increased prevalence of positive bacterial cultures or septic shock on admission to the ICU or with a significant difference in 28 day survival (p. 641 2nd column 1st paragraph).

Although the art of Lorenz et al. (Infection and Immunity 2000 VOl. 68 p. 6398) teaches the association of a specific genotype and a specific inflammatory condition, Lorenz et al. does not provide support for the breadth of the claims. Lorenz et al. was cited on the IDS filed 8/31/2006. Lorenz et al. teaches detecting a genotype of TLR-2 defined by a polymorphic site, as Lorenz et al teaches detection and sequencing of the site which comprises TLR2 Arg753Gln (p. 6399 1st column 3rd full paragraph). Lorenz et al. teaches that the genotype is indicative of increased risk for staphylococcal septic shock (p. 6400 2nd column 2nd paragraph). Septic shock would be a type of inflammatory condition. As this site is associated with staphylococcal septic shock it would be considered a risk genotype.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Quantity of Experimentation and Conclusion

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. The claims are drawn to associations of prognosis of enhanced recovery or increased risk of developing inflammatory conditions by detecting one or more polymorphic sites in TLR-2 in a subject. Therefore the claims encompass analysis of a large number of inflammatory conditions, a large number of polymorphic sites, and the associations to risk of developing or some undefined enhanced degree of recovery.

To practice the invention as broadly as it is claimed, the skilled artisan would have to determine associations in various species and determination of associations of polymorphic regions in a large number of inflammatory conditions.

The skilled artisan would need to perform undue experimentation to determine such an association. Even if the extensive experimentation was performed, there is no assurance that any other additional variants, in any of these species, would be found to be associated with any inflammatory conditions. Such random, trial by error experimentation is considered to be undue and highly unpredictable.

Further, the art indicates that these experimentations do not have a guarantee of success. Specifically Jaen et al. teaches that associations between polymorphisms and inflammatory conditions are cannot be extrapolated to other inflammatory conditions. Halushka et al., Langdahl et al, and Wall et al., teach that associations are population and polymorphic site specific. Woehrle et al. teaches that associations to sepsis are further bacteria type dependent. Sutherland teaches that even at the specific position of 201 of SEQ ID No. 1 and gram positive sepsis, each association must be evaluated to determine if there is a predictably statistically significant association.

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the

claimed method.

Therefore the method as claimed would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Claim Rejections - 35 USC § 112/Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-10, 12-17, and 40-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a correlation of prognosis in a subject of enhanced recovery from an inflammatory condition or increased risk of developing the inflammatory condition by detecting one or more polymorphic sites in the TLR-2

receptor in a subject. The claims are further drawn to determination of one or more polymorphic sites which includes position 201 of SEQ ID No. 1 or a polymorphic site in linkage disequilibrium therewith. The claims are drawn to correlations of the homozygous T genotype at position 201 of SEQ ID No. 1, the T allele at position 201 of SEQ ID NO.1 and the A allele at position 201 of SEQ ID No. 1 in a subject.

The claims are broadly drawn to any polymorphic position of TLR-2 in any subject with the functionality of an association to inflammatory condition. Therefore the genus is drawn to a large number of potential positions in the TLR-2 gene not only in humans, but in any other species. Therefore when the claims are analyzed in light of the specification, the instant invention encompass selecting a subject (human or non human) having one or more of an enormous and wide variety of allelic variants in the TLR-2 gene or allelic variants in linkage disequilibrium with position 201 of SEQ ID No.1. Nucleic acids of such a large genus have not been adequately described by the instant specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of the human TLR-2 gene (SEQ ID NO. 1) and the specific polymorphic variants at position 201 of SEQ ID NO. 1 (p. 2 lines 11-20).

The specification does not define the term subject and as such the claims are drawn to any subject. Any subject would include associations to other species such as gorillas, cats, and dogs. The instant specification has not provided any homologues of

TLR-2 in any organism.

The specification asserts that the polymorphic site may be at SNP 201 or any a polymorphic site in linkage disequilibrium thereto (p. 4 lines 11-12). The specification defines LD as the occurrence in a population of certain combinations of linked alleles in greater proportion than expected from the allele frequencies at the loci (p. 17 lines 1-3). The specification does not teach any variants that are in linkage disequilibrium with the polymorphism at position 201. Therefore the instant specification does not describe any polymorphic position in any organisms which is 95%, 90%, 80%, 75% of the time linked with position 201.

The specification provides examples of the particular genotype at position 201 of SEQ ID NO. 1 in humans and functionally determining an association to a particular inflammatory condition. The specification asserts that the risk genotype may be an indication of an increased risk of not recovering from an inflammatory condition and can including at least one T nucleotide at position 201 of SEQ ID NO. 1 (p. 9 lines 5-9).

Therefore the specification only describes one position (position 201 of SEQ ID NO. 1 in terms of function).

Herein, no common element or attributes to distinguish the polymorphic sites of the genus. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of an association to inflammatory disease are proved.

Further, the art does not provide guidance to sufficiently describe the polymorphic sites, nor does the art teach relevant identifying characteristics or

functional attributes that would distinguish different members of the claimed genus.

Jaen et al. (Arthritis Research and Therapy 2009 Vol.11:R5) teaches that merely having the structure of a polymorphic site of TLR-2 is not sufficient to confirm that a species has the functionality of being correlative to an inflammatory condition. Jaen al. teaches that there was no association between Arg677Trp (e.g. a TLR2 polymorphisms) and susceptibility to infection of arthritis (p. 2 3rd paragraph).

The art teaches that there is a difference in the structure between species, and as such each species would encompass different polymorphic sites. Halushka (Nature Genetics, 1999; 22:239-247) teaches assessing the age or ancestral state of human SNP alleles by obtaining the corresponding orthologous sequence from the closely related great apes (page 244, column 1, paragraph 2). Halushka teaches that although there was a high degree of sequence identity between great ape and human samples (page 244, column 2, paragraph 1), the average nucleotide divergence between human and chimpanzee, gorilla and orangutan was 0.010, 0.012 and 0.021, respectively, and that and that these values are more than ten times greater than the within-population human diversity (page 244, column 2, paragraph 1).

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only one polymorphic sequences of SEQ ID no. 1. The specification does not provide any characteristics that would allow one to

identify any particular portions or fragments or variants of the disclosed sequence that would allow for the determination of risk of developing or prognosis for any type of inflammatory condition.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding polymorphisms linked to position 201 of SEQ ID No. 1, or any polymorphic site of TLR2 in any subject, one of skill in the art cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation or use. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for identifying a polymorphic variation

associated with an inflammatory condition in a subject by detecting the presence of a polymorphism in the subject's TLR-2 gene or any polymorphism linked to position 201 of SEQ Id No. 1.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. It is noted that the claims rejected below under 35 USC 102(b) have also been rejected under 35 USC 112 1$^{st}$ paragraph as not fully described or fully enabled by the specification as originally filed. In the instant case, where the prior art does anticipate particular embodiments of the broadly claimed methods, the prior art is not sufficient to provide an adequate written description of the breadth of the claims, nor is the prior art sufficient to enable the skilled artisan to practice the claimed method in the full scope of the claims.

16. Claims 1-2, 4-9, 14-15, 40, and 42-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Lorenz et al. (Infection and Immunity 2000 VOl. 68 p. 6398).

Lorenz et al. was cited on the IDS filed 8/31/2006

With regard to Claim 1, Lorenz et al. teaches detecting a genotype of TLR-2 defined by a polymorphic site, as Lorenz et al teaches detection and sequencing of the site which comprises TLR2 Arg753Gln (p. 6399 1st column 3rd full paragraph). Lorenz et al. teaches that the genotype is indicative of increased risk for staphylococcal septic shock (p. 6400 2nd column 2nd paragraph). Septic shock would be a type of inflammatory condition. As this site is associated with staphylococcal septic shock it would be considered a risk genotype.

With regard to Claim 2, Lorenz et al. teaches determining a SNP within the TLR-2 gene. As such this position would have some degree of LD with position 201 of the same gene structure. Therefore the SNP of Lorenz et al. would broadly encompass a SNP in linkage disequilibrium with position 201 of SEQ ID NO. 1.

With regard to Claim 4, Lorenz et al. teaches determining the genotype of the TLR-2 (Figure 1).

With regard to Claims 5-7, Lorenz et al. teaches detection that the SNP determination is performed on the nucleic acid of the sample by sequencing and SSCP (e.g. polymerase proofreading method, allele specific PCR, and reading sequence data) (p. 6399 1st column 2nd to last full paragraph).

With regard to Claim 8, Lorenz et al. teaches that the risk genotype of the subject is indicative of increased likelihood of septic shock. As such this would be considered having a poor outcome from an inflammatory condition (e.g. having the presence of the inflammatory condition would be considered a poor outcome).

With regard to Claim 9, Lorenz et al. teaches that the subjects are in the ICU (p. 6398 last paragraph) and as such would be considered critically ill. Lorenz et al. teaches that the presence of the risk genotype is associated to septic shock (p. 6400 2nd column 2nd paragraph) and as such these genotypes would be predictive of severe cardiovascular dysfunction. Specifically septic shock was defined in the instant specification as presence of sepsis plus presence of hypotension (p. 38 lines 15-19). The presence of hypotension would be a type of severe cardiovascular dysfunction.

With regard to Claims 14-15, Lorenz et al. teaches the association of staphylococcal septic shock which would be inflammatory conditions which are associated with Gram-positive sepsis, septicemia, septic shock, SIRS, and fever. It is notes that to be considered as having septic shock the patients had to have 6 inclusion criteria which would be the criteria for SIRs (p. 6399 1st full paragraph).

With regard to Claim 40, Lorenz et al. teaches that the inflammatory condition is associated with staphylococcus, which is a gram positive infection (p. 6400 2nd column 2nd paragraph).

With regard to claims 42-45, Lorenz et al. teaches detection that the SNP determination is performed on the nucleic acid of the sample by sequencing and SSCP (e.g. polymerase proofreading method, allele specific PCR, and reading sequence data) (p. 6399 1st column 2nd to last full paragraph).

With regard to claim 46, Lorenz et al. teaches that the SNP detected (e.g. the risk genotype) is indicative of a gram positive infection (p. 6400 2nd column 2nd paragraph).

## *Conclusion*

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634